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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/836,734	07/02/1997	JACQUES BECKMANN	960-29	6656

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EXAMINER
ZITOMER, STEPHANIE W

ART UNIT	PAPER NUMBER
1634	35

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/836,734	Applicant(s) BECKMANN ET AL.	
	Examiner Stephanie Zitomer	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *9-14, 19, 21, 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,15-18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application status

1. Receipt of the amendment with substitute Sequence Listing abstract filed November 19, 2002 is acknowledged. The pertinent copies of the Table of Contents of the John Libbey book were not included.

2. On reconsideration in view of applicant's request and amendments, claims 5-7, drawn to amino acids, have been added to the claims under prosecution. Claims 9-11 and 19 remain withdrawn from prosecution as drawn to a nonstatutory invention as set forth in paper no. 7 mailed February 27, 1998. Amended claims 12-14 and claims 21 and 22 remain withdrawn from prosecution as drawn to subject matter nonelected by applicant (paper no. 31 filed May 22, 2002). These claims are drawn to a second process of using the product according to PCT Rule 13: a screening method, which differs in kind from the assay method and kit for detecting an LGMD2 disease of claims 15-18. PCT Rule 13 permits only one process of using to be grouped with the product nucleic acid and amino acids and as claims 15-18 were previously examined, the latter claims will be taken as the first process claims.

3. Objections and rejections not reiterated herein from the previous Office action mailed July 19, 2002 have been withdrawn in view of amendments to the claims.

Second request for reference

Informalities

4. The disclosure is objected to because of the following informalities: The SEQ ID NO: for the nucleotide sequence of Figure 2B (human nCL1 cDNA) is missing from the figure and from the figure description (amendment) at page 6. Appropriate correction is required.

Rejection under 35 U.S.C. 112, first paragraph: Lack of written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 15-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method for detecting LGMD2 disease via amplification of nucleotide sequences selected from exons or sequences flanking the exons of the nCL1 gene and comparing amplified sequences with that comprised of SEQ ID NOS:68, 5 and 69 or SEQ ID NOS:1-4 wherein a mutation in an amplified sequence is indicative of LGMD2 disease. The specification describes the identification of mutations in several exons of the nCL1 genes of LGMD2 patients and the corresponding changes in the amino acid sequence (Example 4, pages 13-15). However, the specification does not describe mutations in any other portions of the gene, i.e., no mutations in "flanking sequences of exons" (introns) were found. Furthermore, not all introns have been sequenced (page 5, lines 19-20). Therefore, the written description does not support mutations in flanking sequences as recited in claims 15-17. In addition to enablement the first paragraph of 112 requires a "written description". As set forth by the Court in *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date applicant was in possession of the claimed invention. In view of the absence of any description of any mutations in any part of the nCL1 gene other than in the exons, the skilled practitioner in the art would not have recognized the claimed invention detection method to encompass detection of mutations in sequences flanking exons.

This rejection can be overcome by amending claim 15 by deleting all references to flanking sequences.

Rejection under 35 U.S.C. 112, first paragraph: Nonenablement

6. Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 20 is drawn to a pharmaceutical composition for the treatment of an LGMD2 disease, the composition comprising a nucleic acid sequence of claim 1, a host cell transformed or transfected with a nucleic acid sequence of claim 1 or an amino acid sequence encoded by the nucleic acid of claim 1. The specification at pages 4-5 and 23 discusses gene therapy and use of the claimed pharmaceutical composition for treatment of LGMD2 disease by gene therapy. However, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate with gene therapy encompassed by claim 20. There is no working example or description or even a prophetic example of the claimed pharmaceutical composition, *per se*, or in a treatment of patients with LGMD2 disease. At page 5, first full paragraph, the specification improperly attempts to incorporate an entire book as a description of gene therapy systems, "including adenoviruses, retroviruses and others". Notably, the specification fails to provide any teaching of gene therapy vector construction with the claimed composition comprising a nucleic acid sequence of claim 1, a host cell transformed or transfected with a nucleic acid sequence of claim 1 or an amino acid sequence encoded by the nucleic acid of claim 1. There are no teachings or working examples of pharmaceutical composition preparation, dosages or routes of administration. The examples describe only how to make the nCL1 gene sequences of the claimed invention and how to use them to detect LGMD2 disease. At the time the application was filed, the prior art taught that gene therapy was inoperative at worst and unpredictable at best. For example, Orkin et al. (1995) reviewed the state of the gene therapy art and reported that, among other problems, "[e]fficacy has not been established for any gene therapy protocol". Notably, in this regard, the specification fails to describe dosage and administration and fails to provide any specific protocol for employing the

claimed invention for treatment of LGMD2 disease. The Orkin et al. report also cited "the low frequency of gene delivery to target cells and the lack of definable biochemical or clinical endpoints". Notably, in this regard, the specification fails to identify any biochemical or clinical endpoints of the proposed gene therapy using the claim 20 composition. While the level of skill in the molecular biology art was high at the time of the claimed invention, Ph.D. or higher, the level of unpredictability was also high as demonstrated by the cited references. Absent the required teaching and/or guidance in the specification, it is clear that the skilled practitioner in the art would have required undue experimentation in attempting to practice use of the claimed "pharmaceutical composition for the treatment of an LGMD2 disease" and that the disclosure is nothing more than an invitation to experiment. As the Courts have stated,

> A specification must be more than an invitation to experiment, i.e., applicant may not require persons skilled in the art to perform undue experimentation to achieve a successful result. See *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1933); *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections under 35 U.S.C. 112, second paragraph: Indefiniteness

7. Claims 1-8 and 12-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claim 1 and claims dependent therefrom are confusing because it is unclear whether each sequence in (a), (b) and (c) is intended to be a single sequence among those recited or a single composite sequence. It is suggested to rewrite (a) and (b) as follows:

--(a) a sequence comprised of the sequences, SEQ ID NOS:1-4;

(b) a sequence comprised of the sequences, SEQ ID NO:68, SEQ ID NO:5 and SEQ ID NO:69;--.

Reference to the figures is further confusing because the sequences are entirely separate in the figures.

(b) In claim 1, "said protease" in (c) lacks antecedent basis in (a) or (b). It is suggested to delete "still" and "said" and to identify the protease.

(c) Regarding claims 6, 15 and 16, the phrase "such as" and the word "such" render the claims indefinite because claims containing this phrase or word include elements not actually disclosed (those encompassed by "such"), thereby rendering the scope of the claims unascertainable. See MPEP § 2173.05(d). It is suggested for claim 6 to delete "such as" in line 2 and change "such" in line 4 to --the modified--. In claim 15, "such" may be replaced by --the--.

(d) Claims 15-18 are confusing in reciting nonelected subject matter. The claims must be amended to be drawn to methods and kit employing only the elected primers, SEQ ID NOS:62 and 63.

(e) Claims 16 and 18 are confusing because "derived from" is not defined in the claims or in the specification and one of orinary skill in the art therefore would not be apprised of the scope of primers "derived from" the recited primer sequences.

Rejection under 35 U.S.C. 102(b): Anticipation

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1 and 5-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Sorimachi et al. 1989 (J. Biol. Chem. 264(33):20106-20111). Claim 1(c), drawn to a nucleic acid sequence

comprising a sequence obtained from a sequence defined in Figure 8 or Figure 2 by substitution, deletion or addition of one or more nucleotides wherein the sequence still codes for a protease, is disclosed by Sorimachi et al. at page 20108, Figure 8 which differs from applicant's Figure 8 and Figure 2 sequences by substitutions and/or deletions and/or additions as set forth at page 9 of the specification, lines 17-22. The reference nucleic acid codes for a protease (page 20106, abstract). Regarding the amino acid sequence of claims 5 and 7, Sorimachi et al. also disclose the claimed amino acid sequence encoded by the nucleic acid sequence of claim 1(c) (page 20108, Figure 2) which is a calcuim dependent protease enzyme belonging to the calpain family (page 20106, first text paragraph). That the reference protease is "involved in the etiology of LGMD2 [LGMD2A] disease" is inherent in the Sorimachi et al. protease because the reference and claim proteases are the same and therefore have the same activity absent evidence to the contrary. Sorimachi et al. also disclose the claim 5 amino acid sequence embodiment of claim 6 in that the reference amino acid sequence at Figure 2 (page 20108) contains a sequence "such as", i.e., similar to, the sequence of applicant's Figure 2 or the reference amino acid sequence is modified by deletion, insertion and/or replacement of one or more amino acids of applicant's Figure 2 sequence as set forth at page 9 of the specification, lines 17-22, wherein the reference protease inherently possesses the "calpain activity involved in LGMD2 disease" because the reference and claim proteases are the same and therefore have the same activity absent evidence to the contrary.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Zitomer whose telephone number is (703) 308-3985. The examiner can normally be reached on Monday through Friday from 9:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The official fax phone number for this Group is (703) 308-4242. The unofficial fax number is (703) 308-8724. The examiner's Rightfax number is 703-746-3148.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196. For questions and requests relating to formal matters contact LIE Chantae Dessau at 703-605-1237.

Stephanie Zitomer, Ph.D.
April 4, 2003

STEPHANIE ~~W.~~ ZITOMER
PRIMARY EXAMINER